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WENDY M LEE
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER
HOLLERAN, ANNE L

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/209,023	Applicant(s) PATON ET AL.	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,13 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,13 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed May 23, 2002 is acknowledged. Claims 14-19 were canceled. Claims 1-9, 12, 13 and 34-37 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. This office action contains NEW GROUNDS of REJECTION.

Claim Rejections Withdrawn:

4. The rejection of claims 1-9, 12, 13, 34, and 37 under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Journal of Clinical Oncology, Vol 14, No 3, March 1996 (Baselga I), **Baselga et al.**, Oncology, Vol 11, No 3, March 1997 (Baselga II), **Norton**, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al**. Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186 or **Hudziak et al.**, US Patent 5,770,195, and **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al**. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996, in view of **Singal at al.**, Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view

of **Seifert et al.**, The Annals of Pharmacology, Vol 28, September 1998 is withdrawn in view of the cancellation of claims 14-19, drawn to articles of manufacture.

Claim Rejections Maintained

5. The rejection of claims 1-9, 12-13, and 34-37 under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Oncology, Vol 11, No 3, March 1997, **Norton**, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al.** Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186, in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996 is maintained.

Baselga et al teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (page 46 - page 47, column 1) The effective amount of the combination is less than the sum of the effective amounts of the chemotherapeutic agent and antibody individually (page 46, columns 1

and 3) The efficacy of this method is measured by time to disease progression (page 47, column 1).

Norton teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (See pages S10 8- S109, in the Patient Selection section and Table 1)

Lippman et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast, lung (including non-small cell lung), ovarian, thyroid, salivary gland or prostate cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the extracellular domain, and a chemotherapeutic agent. Lippman et al. further teaches various doses as effective to treat the corresponding cancer. Lippman et al. further teaches co-administration of "any chemotherapeutic" which would include non-anthracycline agents.(columns 9 and 26-29)

Hynes et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 extracellular domain, and a chemotherapeutic agent, cisplatin, which is not an anthracycline derivative. Further, Hynes teaches that the antibody acts synergistically. Therefore, the effective amount of the combination of antibody and chemotherapeutic agent is less than the sum of the effective

amounts of the antibody and the chemotherapeutic agent individually. (page 178, column 2, paragraph 1).

Arakawa et al. teaches a method of treating human breast cancer that comprises administering an anti-ErbB2 antibody and a non-anthracycline chemotherapeutic agent, wherein coadministration enhances the therapeutic effect so that the effective amount is less than the effective amount of the antibody or chemotherapeutic agent when administered individually. (Column 5, line 66-column 6, line 29).

Either of Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al fails to teach the specific chemotherapeutic agent gemcitabine.

Clemons et al., teaches that as a chemotherapeutic, gemcitabine has a higher response rate than many other chemotherapeutic agents and looks promising, and that gemcitabine is effective in combination therapies of breast cancer. (Page 2175, second column and table 8)

Mosconi et al., teaches that gemcitabine is an effective chemotherapeutic, and ideal for combination therapies, that gemcitabine is effective and often synergistic in combination therapies of non-small cell lung cancer.(see for example, abstract)

Carmichael et al. (I) teaches that gemcitabine is ideal for combination therapy and has low toxicity and high response rate, and that gemcitabine is effective in combination therapies of breast cancer.(see for example, abstract).

Carmichael et al. (II) teaches that gemcitabine is ideal for combination therapy and has low toxicity and high response rate, and that gemcitabine is effective in combination therapies of breast cancer.(see for example, abstract).

Tsai et al. teaches that gemcitabine is more effective against cell lines which express high levels of HER2 (see for example, abstract).

Therefore, it would have been *primae facie* obvious to one of ordinary skill in the art at the time of applicant's invention to select the specific non-anthracycline chemotherapeutic agent gemcitabine in the combination therapies of Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al. and one would have been motivated to do so because the prior art teaches that gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. Further, coadministration of antibody and chemotherapeutic agent produces a synergistic therapeutic response, as taught by Hynes et al.

6. The rejection of claims 1-9 and 37 under 35 U.S.C. 103(a) as being unpatentable over **Hudziak et al., US Patent 5,770,195,** and further in view of **Clemons et al.,** European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.,** European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.,** European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.,** Cancer Research Vol. 56, pages 794-801, 1996 is maintained.

Hudziak et al. teaches a method of treatment of any mammal diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the extracellular

domain, and a chemotherapeutic agent which is not an anthracycline derivative. Hudziak fails to teach administration to humans or specific chemotherapeutic agent gemcitabine.

Although Hudziak et al. is silent with respect to the administration of the therapy to human patients, humans would be encompassed by the scope of mammals and the therapy is clearly intended for human use, as the antibody binds a human cell receptor.

Further, Clemons et al., Mosconi et al., Carmichael et al. (I), Carmichael et al. (II) or Tsai et al. teach the desirability of gemcitabine because of it's low toxicity and high response rate as described supra.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to administer the therapy taught in Hudziak et al. to human patients, and one would have been motivated to do so because all receptors and cytotoxic factors are specific human factors and the treatment was ultimately intended for human use, as taught by Hudziak et al in the background of invention. Further, it would have been primae facie obvious to select the specific non-anthracycline chemotherapeutic agent gemcitabine in the combination therapies of Hudziak et al., and one would have been motivated to do so because gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II) or Tsai et al.

7. The rejection of claims 1-9, 12-13, and 37 under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al**, Journal of Clinical Oncology, Vol 14, No 3, March 1996, in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30,

January 1997 (Carmichael I), or **Carmichael et al**. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al**., Cancer Research Vol. 56, pages 794-801, 1996, and further in view of in view of **Hynes et al**, Biochimica et Biophysica Acta, 1994, page 178 is maintained.

Baselga et al in Journal of Clinical Oncology teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody that binds the 4D5 extracellular domain (page 737, last paragraph). Time to response rate was used to measure efficacy (page 738, last paragraph). Baselga et al. fails to teach the administration of the antibody in combination with a chemotherapeutic agent to humans. Baselga et al further fails to teach that the effective amount of the chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually and the selection of the specific chemotherapeutic agent gemcitabine.

As discussed above, Clemons et al., Mosconi et al., Carmichael et al. (I), Carmichael et al. (II) or Tsai et al. teach the desirability of gemcitabine because of its low toxicity and high response rate.

Hynes et al teaches that coadministration of an anti-ErbB2 antibody and a non-anthracycline derivative chemotherapeutic agent produces a synergistic treatment effect. Therefore, the effective amount of the chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to combine the method of treatment of Baselga et al with the method of treatment of either Clemons et al, Mosconin et al, Charmichael et al (I), Charmichael et al (II) or Tsai et al. to make a method that comprised administering an anti ErbB2 antibody and gemcitabine to human patients. The claimed invention may be analyzed in light of In re Kerkhoven (205 USPQ 1069, CCPA 1980) where it was found by the courts that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same purpose: idea of combining them flows logically from their having been taught individually in the prior art."

It is well known in the art as set forth above, that anti-Her2 antibodies are useful in the treatment of cancer, and that gemcitabine is also useful in the treatment of cancer. Furthermore, Hynes et al teaches that coadministration of an anti-ErbB2 antibody and a non-anthracycline derivative chemotherapeutic agent produces a synergistic treatment effect. Methods of inhibiting tumor growth by using chemotherapy are well established and therefore it would be obvious to use chemotherapy treatment in combination with an antibody therapy that has been established to be effective. One would have been motivated to choose gemcitabine because the prior art teaches that it has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al.

8. Claims 1-9 and 12-13, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Journal of Clinical Oncology, Vol 14, No 3, March 1996 (Baselga I), **Baselga et al.**, Oncology, Vol 11, No 3, March 1997 (Baselga II), **Norton**, Seminars

in Oncology, Vol 24, No 4, Suppl 10, August 1997, Lippman et al, US Patent 5,578,482, November 26, 1996, **Hynes et al**. Biochemica et Biophysica Acta 1198, 1994, or Arakawa et al, US Patent 5,783,186 or **Hudziak et al.**, US Patent 5,770,195, and **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al**. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996, and further in view of **Maier et al.**, Cancer Research, Vol. 51, pages 5361-5369, 1991, or **Lewis et al.**, Cancer Immunol. Immunother, Vol. 37, 1993, and **Van Moorsel et al**, Seminars in Oncology, 42/2, Suppl 7, S717-S723, 1997, or **Hansen**, Ann Oncol., Vol. 7, Suppl. 1, pp29, 1996.

Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. teach as applied to claims 1-9 and 12-13 supra. Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II) or Tsai et al. fail to teach specific treatment of bladder cancer or pancreatic cancer using the combination of methods.

In addition to the teachings set forth above, Hynes et al. teaches that HER2 provides an excellent target for cancer therapy, including using anti HER2 antibodies, in any cancer which over expresses HER2. Hynes et al. further teaches that bladder cancer and non-small cell lung cancer over express HER2 (see page 178 and table 2).

Maier et al. teaches that HER2 is over expressed in many cancers, including breast cancer and pancreatic cancer (see page 5361, column 2).

Lewis et al. teaches that teaches that HER2 is over expressed in many cancers, including breast cancer and pancreatic cancer (see page 256, first column)

Van Moorsel et al. teaches that gemcitabine is an effective treatment for bladder, pancreatic, non-small cell lung and breast cancer (see for example, abstract).

Hansen teaches that gemcitabine is an effective treatment for bladder, pancreatic, and non-small cell lung (see entire document).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the treatments of Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. to treat any cancer which over expressed HER2, including non-small cell lung cancer, bladder cancer and pancreatic cancer, because these cancers can all over express HER2, as taught by Hynes et al., Maier et al, and Lewis et al., and further any cancer which over expresses HER2 is ideally targeted by HER2 antibody therapies, as taught by Hynes et al, and further that gemcitabine is also effective for treating non-small cell lung, pancreatic and bladder cancer, as taught by Van Moorsel et al. and Hansen, and also is ideal in combination therapies, as set forth previously.

Arguments

9. Applicant has argued the rejections together, so applicant's arguments are addressed together. Applicant argues that the claimed inventions are patentable over the prior art because

one could not have predicted the safety and efficacy of the combination of an anti-ErbB2 antibody and gemcitabine; because the combination of an anti-ErbB2 antibody and gemcitabine does not exhibit the side effects that occur with the combination of HER2 and anthracycline; and because the combination of an anti-ErbB2 antibody and gemcitabine results in a synergistic effect of inhibiting tumor growth.

Applicant's arguments are not persuasive. The prior art teaches that treatment with either anti-ErbB2 antibodies or gemcitabine are safe and efficacious treatments (see above). Therefore, one of ordinary skill in the art would expect that the combination of the two treatments would be safe and efficacious. The prior art teaches that anthracycline derivatives can produce cardiac toxicity (Singal et al, J. Mol. Cell Cardiol., 27: 1055-1063, 1995; cited in previous Office actions). Furthermore, even if the prior art fails to teach that the combination or an anti-ErbB2 antibody and an anthracycline derivative results in increased cardiac toxicity over the toxicity seen with an anthracycline derivative alone, one of skill in the art would not need to know this to be motivated to choose gemcitabine as a chemotherapeutic agent to combine with an anti-ErbB2 antibody. Because the safety and efficacy of gemicitabine is taught in the art, and because the general concept of combining anti-ErbB2 antibodies with chemotherapeutic agents is taught in the art, the motivation to combine the two treatments is provided by the prior art. A motivation provided in a rejection of a claim as unpatentable over the prior art does not have to be the same as the motivation supplied by the specification. Lastly, a synergistic effect resulting from the combination of two treatments, both known to be useful for the treatment of the same condition, is not in and of itself a surprising result, unless there is a teaching in the prior art that teaches away from the combination of two treatments.

A showing of an additive effect or even synergy is not sufficient to overcome a prima facie case of obviousness, if the results achieved were expected in view of the teachings of the prior art. See MPEP 716.02: "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In Corkhill, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect that is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L- aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.). Furthermore, the prior art teaches an example of a combination therapy involving an anti-ErbB2 antibody and a chemotherapeutic agent where the effect of the combination of the two treatments was synergistic (Hynes et al, above). Thus the demonstration post-filing that the combination of

gemcitabine and an anti-HER2 monoclonal antibody exhibits synergistic anti-tumor effects is not sufficient to overcome the rejection, because it would be expected that the combination of HER-2 with gemcitabine would exhibits synergistic cytotoxicity.

New Grounds of Rejection:

10. Claims 1-9, 12, 13 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al (U.S. Patent 4,994,558; issued Feb. 19, 1991) in view of Hudziak et al (U.S. Patent 5,770,195; cited above).

The claims 1-9, 12, 13 and 37 may be interpreted as encompassing methods where gemcitabine is conjugated to an anti-ErbB2 antibody (see specification, page 31, line 27 – page 32, line 20).

Armour discloses immunoglobulin conjugates of gemcitabine (2'-deoxy-2', 2'-difluorocytidine) with antibodies that bind to tumor cells (col. 7, line 26 – col. 8, line 36, col. 9, line 40 – col. 10, line 20), and teaches that these conjugates may be used to inhibit tumor growth (col. 10, line 21 – col. 11, line 3), and teaches that the immunoconjugates with gemcitabine result in greater efficacy than treatment with gemcitabine alone (col. 10, line 67 – col. 11, line 3). Armour fails to teach conjugates of gemcitabine with anti-ErbB2 antibodies. However, Hudziak teaches anti-ErbB2 antibodies (one embodiment is the 4D5 antibody that binds an extracellular domain of ErbB2) and methods of treatment with anti-ErbB2 antibodies, teaches methods of treatment where the anti-ErbB2 antibody is combined with a chemotherapeutic agent through conjugation (see column 20, claim 19), and teaches that efficacy may be measured by a measurement of response rate (see col. 19, Table 2). Thus, it would have been prima facie

obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Armour with that of Hudziak to make the claimed methods of treatment comprising a combination of an anti-ErbB2 antibody and gemcitabine, where the anti-ErbB2 antibody and gemcitabine are conjugated to each other. One would have been motivated to use the antibody of Hudziak to make an immunoglobulin of Armour because Hudziak teaches that the ErbB2 receptor may be targeted with antibodies to inhibit the growth factor receptor function of ErbB2 and render a tumor more susceptible to cytotoxic factors (col. 5, lines 8-12).

11. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because the phrases "the time to disease progression" and "the response rate" lack antecedent basis.

12. Claims 1, 2, 7-9, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment of cancer, does not reasonably provide enablement for methods of treatment of any disorder characterized by overexpression of ErbB2 receptor or the treatment of a benign tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation

necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claims are broadly drawn to a method for treatment of any disorder characterized by overexpression of ErbB2 receptor, and to a method for treatment of benign tumors.

The specification discloses treatment of human patients who have metastatic breast cancer characterized by overexpression of the ErbB2 receptor. The patients are treated with a combination of an anti-ErbB2 receptor antibody (4D5) and paclitaxel.

Disclosure of treatment of human patients with a single specific type of disorder (metastatic breast cancer characterized by overexpression of the ErbB2 receptor), using a single taxoid and a single type of monoclonal antibody does not support claims which encompass treatment of any disorder characterized by overexpression of ErbB2, including non-malignant tumor disorders and non-cancer disorders, or benign tumors.

There is no guidance or objective evidence that the claimed methods of treatment would be effective for any disorder other than malignant tumors and cancer. The specification fails to set forth any "non-malignant tumor or non-cancer" disorders which are characterized by the overexpression of ErbB2. Further, there is no guidance or objective evidence that the instant treatment would be effective to treat any disorder other than a malignant tumor or cancer which overexpressess ErbB2. The state of the art recognizes the efficacy of ErbB2 antibodies and gemcitabine for treatment of a malignant tumor or cancer. However, neither the specification,

nor the art of record teaches or suggests that either gemcitabine or an anti-ErbB2 antibody may be useful for the treatment for any other disorder.

Thus, due to the absence of suggestion of a different type of disorder, lack of guidance as to what such a disorder might be or how the instant method might function to treat it, the state of the prior art which teaches that the individual components are known to only be useful for malignant tumor or cancer, and that anti-ErbB2 antibodies are useful only in the treatment of cancers that overexpress ErbB2, one of skill in the art would not be enabled to practice the full scope of the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
September 7, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600